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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,717	01/20/2004	Yukun Sun	57783.8004.US00	3780

34055 7590 09/15/2008

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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1656	
MAIL DATE	**DELIVERY MODE**
09/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,717	SUN ET AL.	
	Examiner	Art Unit	
	SAMUEL W. LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-14 and 16-39* is/are pending in the application.

4a) Of the above claim(s) *17-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-14,16 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/13/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1-7, 9-14 and 16-39 are pending.

The amendment filed 6/16/08 (which was submitted through the "power of attorney" of customer NO. 34055, see below) which amends claims 1, 3-4, 9-12 and 16, cancels claims 8 and 15, and adds new claims 37-39 has been entered. The applicants' request filed 6/29/08 for extension of time of one month has been entered. Claims 17-36 remain withdrawn from further consideration by the Examiner (see the Office action mailed 7/31/06). New claims 37-39 drawn to the elected invention. Thus, claims 1-7, 9-14, 16 and 37-39 are examined in this Office action.

The applicants filed (5/28/08) "Revocation of power of attorney with new power of attorney" with the address associated with customer number "34055" before the Patent and Trademark Office (Office) is acknowledged.

Priority

In response to "Priority" section at page 3 of the Office action mailed 7/32/06, applicants clarify that "Applicants confirm that the statement regarding priority in the April 2, 2004 declaration is an inadvertent error. As correctly set forth in the specification as originally filed, the present application claims priority to Chinese Patent Application No. 01126278.8, filed July 19, 2001" (see page 13, 1st paragraph, the applicants' response filed 6/16/08). Due to this submission/clarification, acknowledgment is made of applicant's claim for foreign priority based on the application No. 01126278.8 filed 7/19/2001 in China. It is noted,

however, that applicant has not filed a certified copy of said application as required by 35 U.S.C. 119(b).

Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of the above-mentioned foreign application No. 01126278.8. A new oath, declaration or application data sheet is required in the body of which the present application should be identified by application number and filing date.

IDS

The references cited in the IDS filed 8/13/08 have been considered by Examiner.

Withdrawal of objections and rejections

- The objection to the specification is withdrawn in light of the amendment to the specification.

- The objection to claims 1, 3 and 16 is withdrawn in light of the amendment of these claims.

- The rejection under 35 USC 112, first paragraph (deposit requirement) is now withdrawn in light of the applicants' submission of "Declaration of biological deposit" filed 6/16/08.

- The rejection under 35 USC 102(e) by Rasmussen et al. is withdrawn in light of that the reference does not teach the method of instant claim 1 and 37. See also the "Discussion of art" regarding this.

• The rejection under 35 USC 103(a) by Rasmussen et al. in view of Xia et al. is withdrawn in light of that neither the primary reference Rasmussen et al. (see above) nor Xia et al. teaches or suggests the method of instant claims 1 and 37 and dependent claims therefrom.

New-Objection to specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter in claims 1 and 37 which is "third restriction endonuclease cleavage site" and "N is an integer from 2 to 32". See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). The corresponding correction is required.

New-Objection to claims

Claims 1, 3-4, 9-12, 16 are objected to because, in claim 1, "ligating said digested gene fragment into a vector" should be changed to " ligating said digested gene fragment with a vector.

New-Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-7, 9-14, 16 and 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 lacks antecedent basis for "gene fragment of step (a)" in step b (line 2) because step (a) does not recite "gene fragment". Also, Claim 1, step (c) lacks antecedent basis for "series-linked gene" in the claim. Claims 2-7, 9-14 and 16 which depend from claim 1 also rejected.

Claim 37 is unclear whether or not "a gene" contain the first or/and second restriction endonuclease cleavage site (**RE site**) because the "gene" isolated from naturally occurring source such as chromosome from different species may contain said site(s).

Claim 37 lacks antecedent basis for "the series-linked gene" recited in step c.

Also, claim 37 does not make it clear how the "vector comprising N-copies of a resulting series-linked GLP-1(7-36) gene" can be produced from the claimed method (without repeating step *b*, for example) because the vector in step *b* of claim 37 is considered to be a "vector" containing no nucleotide sequence (gene) encoding GLP-1(7-36) polypeptide. Note that claim 37 doe not set forth that said vector contain said nucleotide sequence or gene. Clarification in this regard is required.

Claims 38-39 which depend from claim 37 are also rejected.

Claim 39 is indefinite becasue neither claim 37 from which claim 39 depends nor claim 39 per se recites "step (e)". Because of this, the recitation "step f" in claim 39 also renders the claim indefinite.

New-Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-14, 16 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement; this is a new matter rejection. The claims contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitations of (i) "N is an integer from 2 to 32" and "third restriction endonuclease cleavage site…" (claim 1), (ii) "N is an integer from 4 to 32" (claim 4); (iii) "N is an integer from 2 to 32" (claim 9), and (iv) "N is an integer from 2 to 32" and "third restriction endonuclease cleavage site…" (claim 37), which as amended into the claims on 6/16/08, are not supported in the specification as originally filed. Applicant can either cancel the new matter or point out specification support for the phrase in the specification as originally filed.

Applicant's amendment filed 6/16/08 asserts that no new matter has been added (page 12, the response). None of the paragraphs listed in the Table of said page 12, Figures 2-4 and Example 5, and originally filed claims 1, 4 and 9 has support for the limitations (i), (ii), (iii) and (iv) set forth above. It is of note that Figure 4 depicts multiple sites of endonucleases, "third restriction endonuclease cleavage site" has different scope than the breadth of Figure 4 thereof because, in the absence of specifying individual "third" ER site, said "*third .. site*" can be broadly interpreted as an additional site in view of the sites disclosed in Figure 4.

Scope enablement

Claims 1-7, 9-14, 16 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of recombinantly producing GLP-1 polypeptide comprising the steps of constructing the expression vector comprising multiple copies of the genes encoding a fusion protein which contains multiple monomeric GLP-1(7-36) polypeptides in tandem, selectively cleaving said fusion protein with a peptidase, e.g., clostripain

which specifically cleave the peptide bond formed by the participation of carboxyl of Arg (see [0126] of the specification) or enterokinase wherein the fusion protein comprises the linker peptide containing the enterokinase (or clostripain)-cleavage site between each monomeric GLP-1(7-36) polypeptide (see [0063]) and purifying the cleaved product, i.e., GLP-1(7-36) monomeric polypeptides, does not reasonably provide enablement for cleavage of the fusion protein *via* trypsin digestion.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Form, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

(1) The scope of the claims/(2)The nature of the invention:

Claims 1 and 37 and dependent claims (e.g., claims 38, 49 and 51) therefrom as written are directed to cleavage of the tandem GLP-1 (7-36) polypeptides wherein the "cleavage" encompasses trypsin digestion. Instant GLP-1(7-36) has amino acid sequence of SEQ ID NO:1 which contains two trypsin cleavage sites at residues 20 (**Lys**-Glu) and residue 28 (**Lys**-Gly). This would results in truncated GLP-1 variant, e.g., GLP-1(7-33). The relative art teaches that C-terminal truncated GLP-1 molecules, e.g., GLP-1(7-33), are inactive, e.g., no effect on stimulating insulin release (see page 784, left column, first paragraph, Li et al. (2008) *J. Peptides Sci*., 14, 777-785). The instant specification provides no factual indicia that trypsinized GLP-1 peptides have biological activity comparable with instant GLP-1(7-36). Although

acylation of internal lysine residues might prevent trypsin cleavage (see [0027]), the claims as written do not set forth the limitation of the "acylation" thereof, but rather the claims are directed to tryptic cleavage in general. Identifying and characterizing bioactive GLP-1(7-36) variants resulted from the trypsinization or partial tryptic digestion needs undue experimentation. Therefore, the scope of claims is outside the bounds of the enablement.

(3) The unpredictability of the art:

Proteolysis of the fusion protein comprising the tandem linked GLP-1(7-36) polypeptides with tryptic digestion is variable and unpredictable because the partial tryptic cleavage does not results in reproducible and bioactive polypeptide (see Li et al. reference above). Furthermore, neither the specification nor the art in the relative field teaches that GLP-1(7-26) which is product of partially trypsin-digested, i.e., cleavage at residues 20 (**Lys**-Glu) of GLp-1(7-36) has the activity.

(4) The state of the prior art:

The art in related field does not teach or provide factual indicia that trypsin digestion of GLP-1(7-36) can produce fully active GLP-1 variant comparable with the bioactive GLP-1(7-36) polypeptide.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the genus stated above, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation would be large and unpredictable. For example, if apply the "partial trypsin digestion" to the claimed method, time of digestion and proper amount of trypsin enzyme used to

ensure completely cleavage peptide bonds between GLP-1(7-36) monomers in the fusion protein produced by instant method are substrate-enzyme dependent (i.e., "case by case basis"); and thus, consequence of the tryptic cleavage is considered to be non-producible. Thus, the quantity of experimentation is large.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of polypeptide and broad scope of disorders encompassed by the claims. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in molecular biology, peptide hormone, endocrinology as well as knowledge in mutagenesis and protein purification. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. In the absence of teaching or direction regarding the core or consensus sequence(s) critical for the function discussed above, and regarding the structure-function correlation which is missing from instant specification and the art in the related field, an unduly level of skill is needed for the skilled artisan in order to identify functional variant nucleotide sequence and thereby to practice the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Thus, the amount and level of experimentation needed is undue.

Conclusion

No claims are allowed.

Discussion of the art

The prior art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

• Rasmussen et al. (WO95175510) teach a method of recombinant production of a tandem repeat (four) GLP-1 polypeptide by PCR synthesis of a cassette of four GLP-1(7-36) genes encoding the polypeptides thereof (Example 1, page 9) wherein the cassette contains two endonuclease sites BamHI and XbaI followed by subcloning GLP-1(7-36) cassette into an expression vector through digestion of the said cassette by said two endonucleases (page 10, last paragraph). The method further comprises transforming the expression vector into E.coli host, expressing the tandem repeat GLP-1(7-36) polypeptide and isolating the polypeptide thereof (page 13). Yet, this reference is not considered to be the 102 or 103 prior art because the reference does not teach or suggest introducing three (first, second and third) different restriction endonuclease sites into terminals of a nucleotide sequence encoding GLP-1(7-36) polypeptide wherein the first and second restriction endonuclease sites form a ""hybrid site" (which is resistant to cleavage by either first or second endonuclease thereof) a required by the instant method. This is also because the prior art method is directed to production of the tandem repeat (four) GLP-1 polypeptide using distinct/different strategy (i.e., pre-synthesis of polynucleotide encoding said cassette encoding said "tandem repeat") from instant method which making the polynucleotide by the disclosed step *a* to step *c* of instant claim 1 or step *a* to step *b* of instant claim 37.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragton, can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

/Samuel W Liu, Ph.D./
Examiner, Art Unit 1656
September 9, 2008

/Karen Cochrane Carlson, Ph.D./
Primary Examiner, Art Unit 1656